AstraZeneca

Date: DEC 2 9 2004 2355 '04 130 1857

Dockets Management Branch
(HFA-305)
Food and Drug Administration
5630 Fishers Lane
Room 1061
Rockville, MD 20852

Re: Docket Number 2004D-0459
Response to FDA Call for Comments
Pharmacokinetics in Pregnancy – Study Design, Data Analysis, and Impact on Dosing and Labeling

Dear Sir or Madam:

Reference is made to the November 1, 2004 Federal Register notice announcing the request for comments on the draft Guidance for Industry, entitled "Pharmacokinetics in Pregnancy – Study Design, Data Analysis, and Impact on Dosing and Labeling."

AstraZeneca has reviewed this Guidance and our comments are attached.

Please direct any questions or requests for additional information to me, or in my absence, to John Boorstein, Regulatory Project Manager, at (302) 886-3682.

Sincerely,

Judith Molt

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Director, Regulatory Affairs
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JM/JAB

Enclosure

2004D-0459 C1

US Regulatory Affairs
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Comments from AstraZeneca on
The FDA Draft Guidance for Industry on Pharmacokinetics in Pregnancy—
Study Design, Data Analysis, and Impact
[Docket No. 2004D-0459]

Comments are summarized below:

General Comments

Comment 1: A risk-benefit assessment of exposing a "reasonable" number of pregnant women to medications in order to study pregnancy pharmacokinetics/pharmacodynamics needs to be considered as compared to taking a more observational approach of monitoring the safety and efficacy of pregnant women exposed to medications by assessing dosage adjustments, diminished or increased efficacy, and clinical overdose (monitoring effects vs. PK parameters).

Comment 2: If studies are deemed mandatory, they should be restricted to products with a long or known record of safety in pregnancy, drugs which do not cross the placenta, administering products using only a single dose of the drug, using lower doses of the drug, decreasing the number of drugs (probe substrates) used in any study subject, and limiting study participants to pregnant women only in second or third trimester. "High-risk" pregnancies are to be excluded.

Comment 3: The document gives a framework for conducting studies in pregnant women. Operationally, given the litigation climate in the US, it is unlikely that such studies would actually be done. There are major operational problems, such as for each drug one wants to study there might be one or two women at a center who need that drug. How then would one accumulate enough patients for the many drugs involved?

Comment 4: It seems that in order to investigate PK, one either has to start or stop the drug, and then obtain blood samples. How would this work for a woman taking a needed medication chronically who is already taking the drug and should not stop?

Comment 5: The issue of long term/delayed effects on the fetus was not mentioned. Although this draft guidance is focused primarily on the PK/PD of drugs in pregnant women, a cursory reference should, at the very least, been made concerning this critical issue.

Comment 6: The guideline may be over-idealistic in terms of what it would be possible to achieve in this patient group. As an example, it may not be possible to obtain the amount of data needed for repeat measures statistics to be applied to longitudinal studies. Similarly, the suggestion of using the 80-125 boundaries to claim 'no effect' would require a study of bioequivalence proportions.

Comment 7: If a PK/PD relationship is established with respect to effect and important safety markers, 'no effect' boundaries should be based on this relationship (ie, the clinical significance of a PK change) rather than the 80-125 boundaries.

Comment 8: Throughout the guideline there is discussion of using the women as their own control. This implies multiple interventions before, during and after the pregnancy. The issue the guidance is trying to address is whether the exposures in pregnant women are discernibly different from those in non-pregnant patients; thus, this is an inter-subject issue and control of intra-subject variability is not necessary or even helpful.

Comment 9: On the subject of protein binding, the practicalities of measuring unbound fraction are legendary and the blood volumes required for this seem inconsistent with this patient group. Couldn't adequate corrections be made by studying in vitro the impact of albumin (etc.) concentration on binding and using the patient's lab values for protein concentration? There needs to be a swing from idealistic/academic to pragmatic.

Comment 10: There seems to be no recognition of the body of human PK-PD information that would be available at the time such studies might be conducted. For example, the suggestion that controls would be healthy females. There cannot be many drugs where there are different doses for male and female patients, so why not use healthy males or healthy all-comers as the control group?

Page Number	**Section Number**	**Comment or proposed replacement text**
1	I – line 32	…advice from experts in fields such as obstetrics, pediatrics, *embryology,* pharmacology, clinical pharmacology…
2	II – line 50	…ones can be exacerbated (e.g., migraine headaches, *diabetes mellitus*), requiring pharmacologic therapy.
2	II – line 68	…treat conditions specific to pregnancy (e.g., oxytocics, *tocolytics,* cervical ripening agents)…
2	II – line 75	…dosage and frequency of administration ~~in~~ *during* pregnancy
3	II – line 101	Add transporters such as p-glycoprotein
3	II – lines 104 to 106	This sentence discusses the need for studies in pregnant women as being similar to the need for other subpopulations. It does not discuss that the ethics are more controversial because of potential risks to the fetus. That is left to the next section, but it needs to be here as well.
4	III – line 121	Is it possible for an IRB to review and endorse a protocol if the risks are not known? Similarly, there are foreseeable difficulties in constructing a patient informed consent form that includes: presenting congenital anomalies which may have been caused by factors other than the drug being studied, and explaining these anomalies in terms that are comprehensible.
4	III – line 127	…and provide *sufficient* data for assessing…

Page Number	Section Number	Comment or proposed replacement text
4	III – lines 146 – 149	The statement that information in the Overall Safety Evaluation section of the PSUR regarding positive or negative experiences during pregnancy is valuable in determining whether to conduct PK studies in pregnant women should be qualified to make clear that because of the numerous caveats regarding post-marketed AE reporting (adverse event recognition, underreporting, biases, estimation of patient exposure, report quality, etc.), a *lack* of reports of untoward pregnancy outcome in the PSUR should *not* be interpreted to imply that the drug is therefore free from risk to the fetus and/or pregnant woman.
4	III – lines 156-166	The guidance does not provide text concerning the characteristics of the PK/PD relationship and the need for PK studies. It should be mentioned that for compounds with a broad therapeutic window, a study in pregnant women should not be needed. In this case, lack of study should not lead to a precautionary label saying that "the PK in pregnancy was not studied", but the Agency may well require a justification on why a study has not been performed. Thus, the bulleted list regarding when to do studies should to read: • Pregnancy is likely to significantly alter the PK of the drug and/or the active metabolite and a posology adjustment may be needed taking the PK/PD-relationship into account. • The drug is prescribed or is likely to be prescribed during pregnancy • Use is expected to be rare....
5	III – line 161	...if there is anticipated or actual *intentional* use of the drug in pregnancy.
5	III – lines 162-164	Cancer chemotherapy agents usually have warnings or contradictions against use in pregnancy; often fetal abnormalities have been found in animal studies.
6	IV A. – line 216	Given the relatively small number of pregnant subjects anticipated in such a study, is it reasonable to expect consistent PK data from subjects in these pre-specified 4-week windows?
6	IV B. – line 234	Suggest using a standard for gestational age (i.e., ultrasound) instead of last menstrual cycle.
7	V A. – line 261	Factors with significant potential to affect the PK of a drug to be studied *and fetal outcome...*

Page Number	Section Number	Comment or proposed replacement text
7	V A. – line 270	The metabolic status of the enrolled subjects needs to be explained further as it is ambiguous.
8	V B. – line 297	Breast-feeding is a related, but separate issue and should be investigated separately.
8	V D. – lines 321 – 328	This section discusses minimizing fetal risk in "pregnant women who volunteer to take the medication for study purposes". It goes on to discuss "pregnant patients who *need* the study drug" (italics added). Careful consideration should be given to whether it is appropriate (from the point of view of impact on the pregnant woman as well as on the fetus) to administer a medication to a pregnant woman who does not gain therapeutic benefit from the medication.
10	VI. A – line 405 - 407	The parenthetical comment is unclear.
12	VII A. – line 464	Does the drug or its metabolites cross the placenta? Is the drug or its metabolites excreted in breast milk and if so, to what extent?